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1804	17

DATE MAILED: 12/04/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 9/6/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire THREE(3) month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-36 are pending in the application.
   Of the above, claims 8-29, 32, 35 AND 36 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-7, 30, 31, 33, AND 34 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims 1-36 are pending in the instant Application. The response to Restriction Requirement filed 9/8/95 (Paper No. 6) has been entered.

Applicant's election with traverse of the invention of group I, claims 1-7, 30, 31, 33, and 34 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the examination of the inventions of groups I-VI would not require a serious search burden because all are similarly classified and because concomitant examination would be more efficient. This is not found persuasive because while inventions I-III, V and VI are all similarly classified, they are drawn to divergent subject matter that would require non-coextensive searches in the non-patent literature. In regard to argument related to efficiency, while such is considered when advancing a restriction requirement, such is not a dispositive factor.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8-29, 32, 35, and 36 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

Claims 1-7, 30, 31, 33, and 34 are currently under examination.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

The claimed invention encompasses the any non-mouse or human embryonic stem (ES) cell. However, the specification fails to provide an enabling disclosure for the preparation and use of non-mouse embryonic stem (ES) cells because the entirety of the specification is drawn towards the preparation of embryonic stem cells from mouse primordial germ cells and the artisan would not have accepted that these teachings would have resulted in the preparation of ES cell cultures from any other species. While the specification indicates that the disclosed methods may be practiced with any animal (see e.g. page 13, lines 15-18), the only guidance present in the specification regarding the culture of

primordial germ cells from any species other than mouse is humans (see specification at pages 22-25), and these teachings are limited to an indication that PGC cells had been established in culture. While applicant asserts that the presentation of PGC cells in culture provide an adequate indication that cultures of human ES cells may be established, the state of the ES cell art fails to support applications contention. For example, as noted by Notarianni et al. (AB1) as of 1990 "the only species other than the mouse for which the derivation of embryonic stem cells has been described is the hamster...**There are, however, significant differences between early embryo development in rodents and in domestic animals such as ungulates, which means that it is not a trivial task to achieve similar results in other species**" (page 51, second paragraph). Thus, the adaptation of methods and results from one species to another was not considered to have been predictable or straight forward with reasonable expectations of success. Further, as noted by Bradley et al., 1992 (R) in discussing "Future Directions" on page 537, the artisan required that putative ES cell lines from species other than mice be validated by passage through the germ line prior to acceptance as true ES cells (see e.g. paragraph bridging pages 537 and 538). Thus, given the limited guidance present in the specification, the absence of any exemplifications directed towards animals other than mice, the indicated state of the prior art, the breadth of the claims, and the unpredictable nature of the ES cell art, it would have required undue experimentation for the artisan to have prepared cultures of ES cells from species other than mouse and limitation to such cells is appropriate.

The specification fails to provide an enabling disclosure for methods of obtaining cells that would have been useful for therapy because the specification fails to provide any guidance regarding how one would have used any cells for any therapeutic purposes. It is understood that embryonic stem cells may be used to prepare chimeric animals, however, such is not normally associated with a therapeutic procedure related to disease states and the specification fails to provide any indication of how any therapies would have been performed. Therefore, the specification fails to provide an enabling disclosure for how to make and use the claimed methods of preparing therapeutic cells.

The specification also fails to provide an enabling disclosure for the invention as defined by claims 33 and 34 because the specification fails to provide any guidance regarding how one would have prepared any therapeutic ES cell derivatives and further fails to provide any guidance regarding how one would have determined whether or not any such derivatives would have been therapeutic.

Claims 1-4, 7, 30, 31, 33, and 34 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 5 and 6 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited compositions comprising mouse embryonic stem cells. See M.P.E.P. §§ 706.03(n) and 706.03(z).

As noted in the statement of the grounds of objection to the specification under 35 U.S.C. § 112, first paragraph, the specification fails to provide an enabling disclosure for the preparation of any embryonic stem cells other than those derived from mice. Thus, while the scope of the claims under instant consideration are drawn to compositions comprising any mammalian embryonic stem cells, the artisan would have been required to have exercised undue experimentation in the preparation of compositions comprising cells other than those derived from mouse.

Claims 2, 3, 5-7, 33, and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is vague and indefinite because it is unclear as to what would render a gene "non-functional".

Claim 3 is vague and indefinite because it is unclear as to what would be required for a gene to have been considered "functional".

Claims 5-7 are unclear because in claims 5 and 7, it is unclear as to whether the "...in amounts to enhance the growth..." limitation is required to apply to all the cited factors or only to the soluble steel factor. The claims are also unclear regarding what would be required for growth to be considered to have been "enhanced".

Claims 33 and 34 are incomplete because the claims are directed to obtained cells but no process step drawn to any obtainment is present.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Evans, 1990 (AB).

The claimed invention is drawn to non-mouse embryonic stem cells that may be passaged at least 20 times and give rise to embryoid bodies and multiple differentiated cell types.

Evans et al. disclose the production of bovine and porcine pluripotential embryonic stem cells. In particular, Evans discloses the use of STO fibroblast feeder layers (see e.g. paragraph bridging pages 9 and 10), an indication of indefinite passage (see e.g. page 10, paragraph "5"; and page 23, section entitled "Differentiation into Embryoid Bodies" wherein it is indicated that cells were used from a cell line that was maintained for 12 months), and that the disclosed cells differentiate into cells representative of all three germ layers and into embryoid bodies (see e.g. page 11, first and second paragraphs). Note that given passaging at 3-4 day intervals, over a 12 month period at least 92 passages were obtained.

Therefore, Evans anticipates what is claimed.

Claims 5 and 6 are rejected under 35 U.S.C. § 102(a) as being anticipated by Matsui et al., 1992 (AA1).

Matsui et al. disclose the preparation of embryonic stem cells from mouse (a mammal) primordial germ cells wherein when said cells are maintained in the presence of membrane bound steel factor (present on feeder layer cells), soluble steel factor, bFGF, and LIF, they form mouse ES cells (see e.g. page 845, first column, first full paragraph; and page 846, second column, first and second paragraphs).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the

subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 2, 3, 30, and 33 are rejected under 35 U.S.C. § 103 as being unpatentable over Evans, 1990 (AB) in view of McMahon et al., 1990 (S).

The claims under consideration are drawn to non-mouse embryonic stem (ES) cells that have a mutation which renders a gene non-functional (claim 3) or which has a functional gene inserted thereto. Also claimed are methods wherein said ES cells are inserted into blastocyst hosts.

The teachings of Evans are delineated above.

McMahon et al. disclose the inactivation of the Wnt-1 gene in mouse embryonic stem cells and the insertion of a functional neo gene (see e.g. Figure 1).

Since Evans discloses ES cells from non-mouse species and the artisan used ES cells for preparing animals that have loss of function or gain of function mutations, it would have been obvious to one of ordinary skill at the time of the invention to have used accepted ES cell technology with non-mouse ES cells.

One would have been motivated to have mutated non-mouse ES cells because Evans indicated that such uses were desirable (see e.g. pages 1-6).

In regard to the method of claim 33, it is noted that ES cells that have been modified and used to prepare animals have been derivatized and evaluated for their ability to alter the phenotype of animals. Thus, by this use it would have been determined as to whether such cells would have been useful for therapies such as correcting or modulating genetic mutations.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 31 is rejected under 35 U.S.C. § 103 as being unpatentable over Evans, 1990 (AB) in view of Pratt, 1987 (T).

The claim under instant consideration is drawn to the use of non-mouse ES cells to prepare aggregation chimeras.

The teachings of Evans are delineated above.

Pratt discloses that the aggregation of cells with morula stage embryos was a standard, art recognized method of preparing chimeric animals (see e.g. section 3.3, page 27).

Since preparation of aggregation chimeras was a standard tool in developmental biology, it would have been obvious to one of ordinary skill at the time of the invention to have used any ES cells

to have prepared such chimeras. One would have been motivated to have prepared such aggregation chimeras because such methods would have resulted in the formation of chimeric animals.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 4, 7, and 34 are free of the prior art of record because the prior art did not indicate the establishment of human embryonic stem cell lines or a reasonable expectation of success in such establishment.

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Stanton whose telephone number is (703) 308-2801. The examiner can normally be reached on Monday through Thursday from 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone can be reached on (703) 308-3153. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1096.

Brian R. Stanton

Brian R. Stanton, Ph.D.
30 November 1995

BRIAN R. STANTON
PATENT EXAMINER
GROUP 1800